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Cost-Effectiveness of Hydroxyurea in Sickle Cell Anemia

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The Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH) demonstrated the efficacy of hydroxyurea in reducing the rate of painful crises compared to placebo. We used resource utilization data collected in the MSH to determine the cost-effectiveness of hydroxyurea. The MSH was a randomized, placebo-controlled double-blind clinical trial involving 299 patients at 21 sites. The primary outcome, visit to a medical facility, was one of the criteria to define occurrence of painful crisis. Cost estimates were applied to all outpatient and emergency department visits and inpatient hospital stays that were classified as a crisis. Other resources for which cost estimates were applied included hospitalization for chest syndrome, analgesics received, hydroxyurea dosing, laboratory testing, and clinic visits for management of patient care. Annualized differential costs were calculated between hydroxyurea- and placebo-receiving patients. Hospitalization for painful crisis accounted for the majority of costs in both arms of the study, with an annual mean of $12,160 (95% CI: $9,440, $14,880) for hydroxyurea and $17,290 (95% CI: $13,010, $21,570) for placebo. The difference in means was $5,130 (95% CI: $60, $10,200;

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***P* = 0.048). Chest syndrome was the next largest cost with a mean difference of $830 (95% CI: $−340, $2,000; *P* = 0.16). The hydroxyurea arm was also associated with lower costs for emergency department visits, transfusion, and use of opiate analgesics. In total, the annual average cost per patient receiving hydroxyurea was $16,810 (95% CI: $13,350, $20,270) and the annual average costs per patient receiving placebo was $22,020 (95% CI: $17,340, $26,710). The difference in means was $5,210 (95% CI: $−610, $11,030; *P* = 0.21). The cost of hydroxyurea with the more intensive monitoring required when using this drug appears to be more than offset by decreased costs for medical care of painful crisis and analgesic use. Although the total cost difference was not significant statistically, these results suggest that hydroxyurea therapy is cost-effective compared to placebo in the management of adult patients with sickle cell anemia. If hydroxyurea can prevent development of chronic organ damage, long-term savings may be even greater. Am. J. Hematol. 64:26–31, 2000.**

Key words: sickle cell anemia; hydroxyurea; cost-effectiveness; medical care costs

INTRODUCTION

The increasing cost of medical care in the U.S. has been a growing concern for insurers, regulators, providers, and patients [1]. This concern has spawned a number of efforts to control medical care costs [2]. These efforts have, in return, given rise to a growing interest in assessing not only the effectiveness, but also the cost-effectiveness, of new therapeutic interventions [3].

The Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH) was a clinical trial conducted to determine the efficacy of a cytotoxic agent, hydroxyurea, in reducing the rate of painful crises in adult patients with sickle cell anemia [4]. It showed that patients who received hydroxyurea had a statistically significant, almost 50% reduction in the rate of crises over 2 years compared to patients who received placebo. This is the first chronic preventive therapy proven effective for the reduction of sickle cell crises. Hydroxyurea, however, is a hematopoietic suppressive drug that requires careful clinical monitoring. This has the potential to increase the costs of care secondary to increased clinic visits and laboratory testing, adding to the cost of the drug itself. A reduction in the occurrence of crisis, however, has the potential to reduce hospitalization and emergency room and clinic visits, as well as reduce costs for analgesics and other symptomatic therapy.

Although the MSH was not initially designed to capture detailed cost data, the design was such that resource utilization could be quantified. The primary outcome measure was number of painful sickle cell crises, whether managed in the outpatient or inpatient setting. Detailed diagnostic and treatment information was collected for each medical contact that the patient had. We were able to use this information to assess resources used in the medical care of the patients on both study arms. Applying costs to these resources allowed us to calculate the differential cost-effectiveness of hydroxyurea compared to placebo for the treatment of patients with sickle cell anemia.

METHODS

The design of the MSH has been presented in detail elsewhere [4,5]. Briefly, it was a randomized, placebo-controlled, double-blind clinical trial involving 299 patients enrolled at 21 sites. Patients enrolled had sickle cell anemia, were at least 21 years old, had at least 3 painful crises the previous year, and were not chronic users of large amounts of opiate analgesics. After randomization to placebo ($n = 147$) or hydroxyurea ($n = 152$), patients were followed up to 2 years and all medical contacts were captured by a system that included a daily diary, monthly telephone calls to the patient, and biweekly visits of the patient to the clinic study site. A painful crisis was defined as a visit to a medical facility that lasted more than 4 h for acute sickling-related pain, which was treated with a parenteral narcotic. The medical facilities could include the emergency department, outpatient clinic or physician's office, or the hospital. Events were validated by medical records and were reviewed by an independent crisis review committee that was unaware of treatment assignment.

In addition to information on occurrence and treatment of painful crises, other information available for our analysis of resource utilization included the amount of oral and parenteral analgesic medication utilized during each crisis, and the maximum tolerated dose of hydroxyurea. Length of hospital stay was recorded for each hospitalization.

To assess the costs of treatment, we applied cost estimates to each unit of resource utilization. The perspective of our analysis is the insurer. Our estimates were based on charges that would be allowed by Medicare, a public payor. Costs used for each component of resource

TABLE I. Costs of Medical Care Per Resource Used (U.S. Dollars)

Resource	Cost	Source
Crisis		
Hospital day		
Painful crisis	$850.00	HSCRC[a]
Chest syndrome	$930.00	HSCRC
Professional fees		
Daily	$45.00	CPT 99232
Admission	$99.00	CPT 99223
Discharge	$54.00	CPT 99238
Ambulatory visit	$80.00	CPT[b] 99215
Emergency department visit	$490.00	Johns Hopkins[c]
Opiate analgesic		
Intramuscular injection	$3.60	CPT 90782
Demerol	$1.50 per 100 mg	AWP[d]
Morphine	$1.60 per 100 mg	AWP
Dilaudid	$20.00 per 100 mg	AWP
Monitoring		
CBC plus WBC differential	$15.00	CPT 85007
Reticulocyte count	$10.00	CPT 85044
Chemistry panel	$15.00	CPT 80012
Urinalysis	$10.00	CPT 81000
Chest X-ray	$32.00	CPT 71020
Clinic visit	$33.00	CPT 99213
RBC transfusion	$150.00	Ref. 16
Hydroxyurea	$3.00 per gram	AWP

[a]Maryland Health Services Cost Review Commission.
[b]American Medical Association Current Practice Terminology (national average).
[c]Johns Hopkins Hospital Billing Data.
[d]Average Wholesale Price (national).

utilization are shown in Table I. Hospital inpatient costs were based on data obtained from the Maryland Health Services Cost Review Commission (HSCRC) database [6]. The Commission maintains a summary of all discharges from acute-care, nonfederal hospitals in Maryland. For our analysis, we determined average daily charge for all patients 21 years old or greater with a principal ICD-9-CM discharge code of 282.62 (sickle cell anemia with crisis) during calendar years 1993 and 1994 ($N = 1779$). The average daily rate for chest syndrome was based on a principal ICD-9-CM diagnosis code of 282.62 and a secondary ICD-9-CM code of 486.0 (pneumonitis without an infecting organism identified) during the same calendar years ($N = 94$).

To calculate costs, the number of days of hospitalization was multiplied by the average daily charge from the HSCRC database, adjusted for inflation to their equivalent 1995 dollars using the health care cost component of the Consumer Price Index [7]. Added to this were daily professional fees based on the Relative Volume Units of the American Medical Association current practice terminology (CPT) coding [8]. The cost of an emergency department visit was based on the charges for an emergency department visit at the Johns Hopkins Hospital in 1995 for a principal diagnosis ICD-9-CM code of 282.62 ($N = 587$). All accumulated charges were used including professional fees. A nonemergency department ambulatory visit to an outpatient clinic or physician's office for painful crisis was based on a complex visit (CPT: level 5) for an established patient of at least 4 h (average = 6 h). For oral hydroxyurea dosing, we used the national average wholesale price and the maximum tolerated dose for each patient [9]. Dosing of opiate analgesic therapy in the outpatient setting was recorded, and the national average wholesale price [9] was applied to this dosing information. Administration costs were based on the CPT code for intramuscular or percutaneous injection. Red blood cell transfusions in the outpatient setting were recorded, and the cost of a transfusion was based upon a nationally defined average. Analgesic treatment or transfusion occurring during a hospitalization was not tabulated since these costs were assumed to be bundled into the inpatient cost of care.

Since this was a controlled clinical trial, medical visits for monitoring of therapy were dictated by the trial. These controlled, trial-based resources, therefore, could not be used as representative of clinical practice. Instead, we assumed for our analysis that a patient starting on hydroxyurea would be monitored according to the following schedule: every 2 weeks for 2 months, thereafter every month for 4 months, and then every 3 months as long as hydroxyurea was received. Monitoring would include a clinic visit of low complexity (CPT: level 2) for an established patient, a complete blood count, WBC differential and reticulocyte count at each visit, and a chemistry panel four times during the year. A urinalysis would be done twice a year and a chest X-ray annually. For patients who do not receive hydroxyurea, monitoring would include low-complexity clinic visits every 3 months with laboratory testing including a complete blood count and WBC differential, a urinalysis and chemistry panel twice a year, and a chest X-ray annually.

Analysis was done by multiplying the units of resource utilization by their corresponding costs for each person in the study. An average cost was calculated for the patients in each study arm with a 95% confidence interval estimated based on the standard error of the mean [10]. The difference in the averages was calculated with a 95% confidence interval estimated based on the standard error of the mean difference. All costs were annualized for this analysis based on the length of follow-up for each patient. Statistical comparisons of costs were done using the nonparametric Wilcoxon rank-sum test [10]. *P* values are two-tailed.

RESULTS

There were no statistically differences ($P > 0.05$) between the hydroxyurea and placebo assigned patients in regard to age, sex, race, annual crisis rate, previous com-

TABLE II. Characteristics of the Patients in the MSH at Baseline by Treatment Group

	Hydroxyurea (N = 152)	Placebo (N = 147)
Age (mean years)	30	31
Sex (% of patients)		
Male	50	50
Female	50	50
Race (% of patients)		
Black	98	98
Other	2	2
Annual crises before treatment (% of patients)		
3–5	44	44
6–9	26	21
≥10	30	35
Previous complications (% of patients)		
Chest Syndrome	66	65
Ankle Ulcer	31	33
Aseptic Necrosis	20	22
Blood counts (mean)		
Hemoglobin (g/dL)	8.4	8.5
White cells (10^{-3}/mm^3)	12.6	12.3
Platelets (10^{-3}/mm^3)	468	457

TABLE III. Annual Costs for Medical Care for the MSH (U.S. Dollars)

Resource	Hydroxyurea mean (95% CI)	Placebo mean (95% CI)	Difference[a] mean (95% CI)
Crisis			
Hospitalization			
Painful crisis	12,160 (9,440, 14,880)	17,290 (13,010, 21,570)	5,130 (60, 10,200)
Chest syndrome	1,350 (390, 2,300)	2,180 (1,500, 2,860)	830 (−340, 2,000)
Ambulatory visit	30 (20, 40)	50 (30, 70)	20 (−5, 50)
Emergency department	1,490 (1,090 1,890)	2,070 (1,590 2,540)	570 (−50, 2,000)
Opiate analgesics	30 (70, 150)	40 (80, 200)	10 (−30, 120)
Monitoring			
Laboratory	300	130	−170
Clinic visits	330	130	−200
Transfusion	140 (60, 220)	200 (80, 320)	60 (−90, 200)
Hydroxyurea	1,050 (970, 1,130)	0	−1,050 (−970, −1,130)
Total	16,810 (13,350, 20,270)	22,020 (17,340, 26,710)	5,210 (−610, 11,030)

[a]Difference = placebo − hydroxyurea.

plications of sickle cell disease, or blood counts at baseline (Table II).

Calculated costs are shown for each arm of the study stratified by the individual component of resource used (Table III). Hospitalization for painful crisis accounted for the majority of costs in both arms of the study, an annual mean of $12,160 (95% CI: $9,440, $14,880) for hydroxyurea users and $17,290 (95% CI: $13,010, $21,570) for placebo users. The difference in average hospitalization costs between the two arms was $5,130 (95% CI: $60, $10,200; $P = 0.048$). Chest syndrome was the next largest cost with a mean difference of $830 (95% CI: $−340, $2,000; $P = 0.16$). The hydroxyurea arm was also associated with lower costs for emergency department visits ($570; 95% CI: $−50, $200; $P = 0.01$), other ambulatory visits ($20; 95% CI: $−$5, $50; $P = 0.84$), and use of opiate analgesics ($10; 95% CI: $−30, $120; $P = 0.009$) and transfusion ($60; 95% CI: $−90, $200; $P = 0.65$). Monitoring of therapy and hydroxyurea dosing added to costs in the hydroxyurea arm. In total, the average cost per patient receiving hydroxyurea was $16,810 (95% CI: $13,350, $20,270) and the average costs per patient receiving placebo was $22,020 (95% CI: $17,340, $26,710). The mean difference was $5210 (95% CI: $−610, $11,030; $P = 0.21$).

DISCUSSION

The MSH demonstrated a significant (almost 50%) reduction in the rate of painful crises in adult patients with sickle cell anemia receiving hydroxyurea when compared to patients receiving placebo [4]. Our analysis of associated resource utilization and applied costs also suggests a reduction in the cost of medical care for those patients receiving hydroxyurea. On average, the additional costs of hydroxyurea therapy and monitoring of safety were more than offset by a lowering of costs in all other clinical care components that we examined, particularly in the need for hospitalization. The statistical comparison of total costs between the hydroxyurea and placebo receiving patients demonstrated a difference that was significant with a $5,210 increment in means between the two study arms. The distribution of costs are skewed, with a small number of patients with very high costs who influence the value of the mean in each study arm. Nevertheless, the mean or average cost is probably a better measure from a payer's perspective since the high costs of these outliers must be paid, and the 95% confidence intervals give the payor a reasonable estimate of the range in costs that could be expected in most patient samples.

The MSH was designed to have an adequate statistical power to detect a meaningful difference in crisis rates. It was not designed to statistically test differences in medical care costs. The lower mean costs for crises, transfusion, and analgesics associated with hydroxyurea compared to placebo, with 95% confidence intervals that overlap to only a small degree, suggest that medical care costs are substantially lowered in hydroxyurea users. Total costs include a component that increases costs due to

the drug itself plus monitoring and a component that decreases costs due to fewer crises and associated medical care. In addition, the largest cost benefit component (crisis) and the largest cost-increment component (drug and monitoring) for hydroxyurea therapy both add to the variation and reduce the differential in total cost. This explains why there was a substantial difference between hydroxyurea- and placebo-receiving patients in the cost for these components and in the total cost. Currently there are no better data available in which to assess comparative costs. Although we believe that our results are supportive of the dominant cost-effectiveness of hydroxyurea therapy (e.g., hydroxyurea is both effective and reduces costs of medical care), it will require further data on a larger population to make more precise estimates of the costs.

Our analysis is based principally, though not entirely, on costs incurred by patients with sickle cell anemia in Maryland. Hospitalization costs, the largest resource utilized, was based on the statewide Maryland HSCRC database. Approximately 17% of the hospitalizations were at one of the two University hospitals in Maryland, with the remaining 83% at various urban, suburban, and rural hospitals. The outpatient visits, laboratory testing, radiology and drug costs were based on national averages. Emergency department costs were based on a single university hospital in Maryland and may be the cost least likely to be generalizable nationally. Our costs of $22,020 per year for placebo-receiving patients are substantially lower than the estimated charges of $112,000 per year from a 1991 assessment of health care use in clinical practice in Philadelphia in adult patients with sickle cell anemia [11]. The principal difference was in the cost of hospital admissions per year. There were half as many annual admissions in the placebo arm of the MSH than in the Philadelphia study, and the average length of hospital stay was only about half as long. There are at least three possible explanations for this difference. First, though patients enrolled in the MSH had a history of at least three crises in the year prior to enrollment, both "regression to the mean" and a "volunteer selection effect" may have resulted in lower crisis rates for the patients who consented to be in the study. Second, it is possible that in the setting of a controlled clinical trial, a "placebo effect" associated with the more intensive care of the patient on both arms of the study contributed to a lower rate of crises requiring hospitalization. Third, it is possible that hospital costs in Maryland are lower than in Philadelphia. We would note, however, that the Maryland HSCRC data link charges to actual costs of care to a greater extent than in other states [6]. It is also an all-payer state, meaning that all third-party payers are charged the same rate, important since many patients with sickle cell anemia have Medicaid as their insurer. Therefore, we believe that the Maryland hospital cost data represent a fair measurement of actual costs of care.

Over periods of time longer than the 2 years of this trial, it is possible that differences in the rates of death, stroke, renal failure, or other serious vascular events might emerge between the users and nonusers of hydroxyurea. If so, these could have implications for the medical care costs associated with hydroxyurea use. Our analysis was also limited to direct medical care costs; we did not assess indirect costs related to quality of life or other nonmedical factors. If quality of life is improved because of reduced frequency of painful crisis, there may be other cost-related benefits that accrue through the use of hydroxyurea, such as the ability to maintain employment.

It is also important to note that a clinical trial is a well-controlled setting in which patients may have additional incentives to comply with therapy. Approximately 8% of patients in the MSH discontinued therapy permanently because of various reasons including pregnancy, myelotoxicity, and need for transfusion therapy. Patient compliance with hydroxyurea was suspected to be less than 50% in as many as 15% of patients [12]. In actual clinical practice, the difference in costs may not be as marked as in the MSH if noncompliance or cessation of therapy is even more frequent.

It is currently estimated that there are approximately 5,000 adult patients in the U.S. with sickle cell anemia who meet the MSH eligibility criteria (e.g., three or more annual crises) and may be candidates to receive hydroxyurea as prophylactic therapy for painful crisis [13]. At a savings of $5,210 per patient per year, this could translate into a total cost savings of almost $26 million across the U.S. if this drug was used in all these patients. Hydroxyurea cannot currently be recommended for children or for adults with sickle cell anemia who average fewer than three crises per year since it has not yet been proven efficacious and safe in these groups. If it is ultimately shown to provide a benefit in children, there may be substantial medical care cost implications associated with reduction of crises and vascular events starting early in life. Although hydroxyurea is effective in reducing the rate of painful crises, it is a palliative not a curative therapy. In contrast, bone marrow transplantation is potentially curative [14], thereby leading to potentially greater savings over a lifetime compared to hydroxyurea therapy [15]. Bone marrow transplantation can be associated with morbidity and mortality, however, and the initial costs of bone marrow transplantation are comparatively large. A formal cost-effectiveness analysis would need to be done when sufficient data are available regarding this intervention in sickle cell anemia.

In summary, our analysis of resource utilization suggests that use of hydroxyurea to decrease the frequency of painful crises in patients with sickle cell anemia will

result in reductions in the cost of management of crises that more than offset the increased costs associated with the drug and its clinical monitoring. Factors affecting variation in costs and effective sample size prevented the detection of a statistically significant difference in total costs. With this important caveat, our cost analysis of the MSH data indicate that hydroxyurea is not only effective but that it may also be cost-effective compared to placebo in the prevention of painful crises in sickle cell anemia.

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